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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/800,016 | 03/05/2001 | Dean K. Pettit | 3253 | 5188 |

500 7590 02/23/2005

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| EXAMINER | |
|---|---|
| SPECTOR, LORRAINE | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1647 | |

DATE MAILED: 02/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/800,016 | PETTIT ET AL. | |
| | Examiner | Art Unit | |
| | Lorraine Spector, Ph.D. | 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *12 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-7,9-13 and 16-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-13 and 16-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/12/2004 has been entered.

The Examiner acknowledges that the request filed on 3/1/2004 was a request for continued examination, and not a CPA.

Claims 1-7, 9-13 and 16-24 are pending and under consideration.

Applicant's traversal of the previous art rejections is moot in view of the art rejections as now applied. It is noted that the claims allow/require the presence of both EDTA and benzyl alcohol.

### *Rejections Over Prior Art*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7, 9 and 16-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over the LEUKINE® Sargramostim product insert, cited by applicants in paper number 5, in view of U.S. Patent Number 5,217,954 (Foster et al.) and U.S. Patent Number 6,620,784 (Ferrara et al.), and in the case of claims 4-8, further in view of U.S. Patent Number 5,545,536 (Kaushansky et al.).

The Leukine® patient insert teaches that sargramostim is provided in liquid form at a concentration of 500 mcg/mL (micrograms per milliliter), with 1.1% benzyl alcohol, 40 mg/mL mannitol, 10 mg/mL sucrose, and 1.2 mg/mL tromethamine (third paragraph of insert). At the bottom of the first column of the third page, and again on the fifth page, there are warnings that preparations containing benzyl alcohol, including both LEUKINE® liquid and lyophilized LEUKINE® reconstituted for injection, should not be used in neonates. The LEUKINE® (sargramostim) insert differs from the claims in that it does not teach inclusion of EDTA, nor the inclusion of TRIS-HCL.

Ferrara et al. teach the use of both benzyl alcohol and EDTA in therapeutic compositions of VEGF-E, another cytokine; see column 47, lines 7-30, for example. They state that EDTA is a chelating agent (line 29), and that benzyl alcohol is a known antimicrobial agent (col. 48, lines 19-21).

Foster et a. teach the use of EDTA as a chelating agent for the stabilization of bFGF, another cytokine. At column 1, they state that the EDTA "stabilizes this protein against oxidation of its free cysteine residues or metal-induced aggregation, thereby preserving the homogeneity of the purified product."

The use of TRIS as a buffering agent in protein and pharmaceutical preparations is notoriously old and well known in the art. For example, Kaushansky et al. teach the use of TRIS buffers in the isolation of GM-CSF, see for example column 17.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to have modified the sargramostim preparation disclosed in the LEUKINE® insert by the addition of EDTA, as taught by both Ferrara et al. and Foster et al. One of ordinary skill in the art would have been motivated to make the addition in order to prevent oxidation of the GM-CSF protein, and would have been motivated to do so in view of

the recognition in the art that EDTA is generally useful for such in compositions comprising cytokines, as evidenced by Ferrara and Foster. The specific concentration of EDTA to be added would be easily determinable, and is considered well within the purview of routine experimentation by the ordinary pharmacologist. It further would have been obvious to use TRIS as a buffering agent, as it is notoriously old and well known in the art as such, for example see Kaushansky. Accordingly, the invention, taken as a whole, is *prima face* obvious over the prior art.

The Examiner notes the results disclosed at page 13 of the specification. The results therein are not considered to be "unexpected", as the person of ordinary skill in the art reading the above-cited references would have expected GM-CSF stored in the presence of EDTA to more stable than that without. It would appear that the results therein merely compare the presence to the absence of EDTA, and do not compare the preparations containing EDTA to comparable prior-art preparations lacking EDTA. Further, as EDTA and benzyl alcohol were known to work by different mechanisms (the former directly preventing oxidation of proteins and therefore directly stabilizing them, the latter preventing microbial growth), it would be expected that a GM-CSF composition comprising EDTA would be more stable than one without. Accordingly, the invention, taken as a whole, is *prima face* obvious over the prior art.

Claims 10-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over the LEUKINE® Sargramostim product insert, cited by applicants in paper number 5, in view of U.S. Patent Number 6,620,784 (Ferrara et al.) , and U.S. Patent Number 5,217,954 (Foster et al.), as cited in the rejection of claims 1-7, 9 and 16-24 above, and further in view of U.S. Patent Number 6,500,418 B1 (Dieckgraefe et al.)

Claims 10-13 are drawn to methods of treating IBD, including Crohn's disease, using the composition of claim 1. The references cited in the rejection of claims 1-9 do not specifically disclose treatment of IBD/Crohn's disease with GM-CSF. Dieckgraefe et al. disclose and claim treatment of Crohn's disease with GM-CSF, see claims 1 and 21, especially. It therefore would have been obvious to the person of ordinary skill in the art to substitute the composition of claim 1 in the method of Dieckgraefe et al. to attain the known and expected benefits of treating

Crohn's disease with GM-CSF, as disclosed by Dieckgraefe et al. Accordingly, the invention, taken as a whole, is *prima facie* obvious over the prior art.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

U.S. Patent Number 5,902,785 is cited as another example of a patent in which EDTA and benzyl alcohol are suggested together for use in compositions comprising cytokines; see for example column 8, lines 38-40.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Ms. Brenda Brumback, at telephone number 571-272-0961.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to 571-273-8300. Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lorraine Spector

Lorraine Spector, Ph.D.
Primary Examiner

2/19/2005